IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Jay BUA

Title: **REDUCTION OF BREAST DENSITY WITH 4-HYDROXY TAMOXIFEN**

Appl. No.: 10/734,644

Filing Date: 12/15/2003

Examiner: B. Fetterolf

Art Unit: 1642

Confirmation Number: 9030

DECLARATION OF JEAN L. FOURCROY, M.D. UNDER 37 C.F.R. § 1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Jean L. Fourcroy, M.D., do hereby declare and state as follows:

1. I received an M.D. degree from the Medical College of Pennsylvania in 1974, a Ph.D. from the University of California at San Francisco in 1977, and a Masters in Public Health from the Medical College of Wisconsin in 1999. I completed surgery and urology residencies at George Washington University Medical Center and earned Board Certification in Urology in 1981. I was a Medical Officer with the Food and Drug Administration for almost 20 years. In this capacity I was involved with many aspects of the regulatory process, including the development of new drugs, devices and issues surrounding supplements. My research has included a wide range of developmental and reproductive biology. I am currently a regulatory consultant in areas of urology and endocrinology. I have been appointed to the Board of the U.S. Anti-Doping Agency and am an active member of the American Urological Association, the American Society of Andrology, and Past President of the American

Medical Women's Association. I serve on the editorial board of NCI/PDQ Prevention and Screening. My CV is attached.

2. From time to time I have been retained by Ascend Therapeutics, Inc. as a consultant to provide my professional opinion on various matters. Ascend Therapeutics, Inc. has retained me to prepare this Declaration, for which I am being compensated for my time at my usual consulting rate of $300/hour.

3. I understand that Ascend Therapeutics, Inc. is the licensee of U.S. Patent Application 10/734,644 ("the application"), which I have reviewed and which I understand is directed to reducing breast density using 4-hydroxy tamoxifen.

4. I have reviewed the Office Action mailed April 10, 2007, where the Patent Office Examiner states that the method described in the application is obvious in view of (i) Atkinson *et al.*, *Cancer Epidem., Biomarkers & Prev. 863-66* (1999); (ii) Boyd *et al.*, *J. Nat. Cancer Inst.* 87: 670-75 (1995); (iii) Kolb *et al.*, *Radiology* 225: 165-75 (2002); (iv) Mauvais-Jarvis *et al.*, U.S. Patent 4,919,937; (v) Mauvais-Jarvis *et al.*, *Cancer Res.* 46: 1521-25 (1986); and (vi) Yamaguchi *et al.*, U.S. Patent 5,820,877).

5. I provide the following statements on this issue, which I understand may be used to support the application. The opinions expressed here are based on my knowledge and experience in the field.

6. I understand the Patent Office Examiner's position to be based on the following: (i) Atkinson describes the use of tamoxifen to reduce mammographic breast density, (ii) the Mauvais-Jarvis patent states generally that 4-hydroxy tamoxifen could be administered transdermally to treat benign or cancerous conditions of the breast; and (iii) the Mauvais-Jarvis patent (and other publications) mentions that 4-hydroxy tamoxifen is an active metabolite of tamoxifen. Apparently, the Patent Office Examiner believes that, because 4-hydroxy tamoxifen is an active metabolite of tamoxifen, it would have been obvious to use 4-hydroxy tamoxifen to treat conditions that have been treated with tamoxifen, such as in the Atkinson method to reduce mammographic breast density. I must disagree.

7. The Atkinson paper describing the use of tamoxifen to reduce mammographic breast density does not refer in any way to the percutanous use of 4-hydroxy tamoxifen for the reduction of breast density. While the Mauvais-Jarvis patent and publication describe transdermal 4-hydroxy tamoxifen preparations, they do not show methods for reducing breast density. Moreover, it is not possible to extrapolate from Atkinson's use of tamoxifen to the use of 4-hydroxy tamoxifen described in the application, or from Mauvais-Jarvis' general disclosure to the reduction of breast density.

8. It is important to understand that tamoxifen and 4-hydroxy tamoxifen are distinct agents, each with unique safety and efficacy profiles. For example, tamoxifen manifests different biological activities in different cells. It is dependent upon cytochrome P450 enzymes for metabolism to a more active metabolite, such as 4-hydroxy-tamoxifen, and it is a potent rat liver carcinogen, unlike 4-hydroxy tamoxifen. *See, e.g.*, Carthew *et al.*, *Archives of Toxicology* 75: 375-80 (2001); Sauvez *et al.*, *Carcinogenesis* 20: 843-50 (1999).

9. For both tamoxifen and 4-hydroxy tamoxifen, the final response element at the cellular level is dependent on the unique conformation of the estrogen receptor in the individual cell type. *See, e.g.*, Wijayaratne *et al.*, *Endocrinology* 140: 5828-840 (1999); Giambiagi *et al.*, *J. Steroid Biochem.* 30: 213-17 (1988). Estrogen receptor binding by tamoxifen recruits different co-factors than estrogen receptor binding by 4-hydroxy tamoxifen. For example, tamoxifen initiates apoptosis in p53(-) normal human mammary epithelial cells, while 4-hydroxy tamoxifen does not. *See, e.g.*, Dietze *et al.*, *J. Biological Chemistry* 276: 5384-394 (2001). On the other hand, 4-hydroxy tamoxifen inhibits estrone sulphatase activity in mammary cancer cell lines, while tamoxifen has little effect in this regard. *See, e.g.*, Chetrite *et al.*, *Anticancer Research* 13: 931-34 (1993).

10. The literature illustrated by the publications that I have cited above demonstrate that tamoxifen and 4-hydroxy tamoxifen have different modes of action. Thus, persons versed in this field understand that knowing that tamoxifen is useful in a given

therapeutic regimen does not provide a reasonable basis for expecting that 4-hydroxy tamoxifen would be useful for the same purpose.

11. I also understand the present invention to provide significant advantages over the state of the art, particularly over the use of tamoxifen to reduce breast density. This is because percutaneous 4-hydroxy tamoxifen offers important safety improvements. While the side effects of tamoxifen were known, it was not known that 4-hydroxy tamoxifen would be useful to reduce breast density. Thus, the application describes a significant advance in methods of reducing breast density.

12. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that willful, false statements may jeopardize the validity of the application or any patent issued thereon.

July 6, 2007
DATE

Jean L. Fourcroy, M.D.